Familial skin cancer syndromes

Increased risk of nonmelanotic skin cancers and extracutaneous tumors

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Learning objectives
After completing this learning activity, participants should be able to explain how to screen patients for inherited nonmelanoma skin cancer risk; discuss new developments in next generation sequencing and new approaches for genetic testing of patients with nonmelanoma skin cancer; and develop an appropriate management plan for a patient with nonmelanoma skin cancer.

Disclosures
Editors
The editors involved with this CME activity and all content validation/peer reviewers of the journal-based CME activity have reported no relevant financial relationships with commercial interest(s).

Authors
The authors involved with this journal-based CME activity have reported no relevant financial relationships with commercial interest(s).

Planners
The planners involved with this journal-based CME activity have reported no relevant financial relationships with commercial interest(s). The editorial and education staff involved with this journal-based CME activity have reported no relevant financial relationships with commercial interest(s).

Nonmelanoma skin cancers (NMSCs) represent the most common malignancies worldwide, with reported incidence rising each year. Both cutaneous squamous cell carcinoma (SCC) and basal cell carcinoma (BCC), as well as other NMSCs, represent complex diseases with a combination of environmental and genetic risk factors. In general, hereditary cancer syndromes that increase the risk of NMSC fall under several broad categories: those associated with immunodeficiencies, those that affect skin pigmentation, and those that perturb key molecular pathways involved in the pathogenesis of NMSCs. Many of the syndromes are also associated with extracutaneous manifestations, including internal malignancies; therefore, most require a multidisciplinary management approach with a medical geneticist. Finally, dermatologists play a critical role in the diagnosis and management of these conditions, because cutaneous findings are often the presenting manifestations of disease. (J Am Acad Dermatol 2016;74:437-51.)

Key words: Bloom syndrome; dyskeratosis congenita; genetic testing; Gorlin syndrome; Muir–Torre syndrome; nonmelanoma skin cancer; oculocutaneous albinism; Rothmund–Thomson syndrome; Werner syndrome.

INTRODUCTION

Nonmelanoma skin cancers (NMSCs) represent the most common malignancies in the United States, making up 96% of all skin cancers and accounting for 2 to 3 million cases each year.[1] Like melanoma, cutaneous squamous cell carcinoma (SCC) and basal cell carcinoma (BCC) represent complex diseases influenced by both the external environment and inherent genetics. While tumor development in both often occurs sporadically and is strongly associated

From the Department of Dermatology, Stanford University Medical Center.
Supported by a Stanford University Medical Scholars Research Fellowship (Ms Jaju) and the Howard Hughes Medical Institute (Ms Ransohoff).
Conflicts of interest: None declared.
Accepted for publication August 6, 2015.
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0190-9622/$36.00

http://dx.doi.org/10.1016/j.jaad.2015.08.073
Date of release: March 2016
Expiration date: March 2019

Abbreviations used:

5-FU:	5-fluorouracil
ADA1:	adenosine deaminase 1
ADA-SCID:	adenosine deaminase severe combined immunodeficiency
BCC:	basal cell carcinoma
BCNS:	basal cell nevus syndrome
BDCS:	Bazex-Dupré-Christol syndrome
BLM/RECQL3:	Bloom syndrome, RecQ helicase-like
C10Orf11:	chromosome 10 open reading frame 11
C16Orf57:	chromosome 16 open reading frame 57
DFSP:	dermatofibrosarcoma protuberans
DC:	dyskeratosis congenita
EV:	epidermodysplasia verruciformis
EVER1:	epidermodysplasia verruciformis 1
EVER2:	epidermodysplasia verruciformis 2
HNPCC:	hereditary nonpolyposis colon cancer
HPV:	human papillomavirus
IHC:	immunohistochemistry
MSI:	microsatellite instability
MMR:	mismatch repair
MTS:	Muir–Torre syndrome
MSSE:	multiple self-healing squamous epithelioma
MLH1:	MutL homolog 1
MSH2:	MutS homolog 2
MSH6:	MutS homolog 6
NK:	natural killer
NMSC:	nonmelanoma skin cancer
OCA:	oculocutaneous albinism
OCA2:	oculocutaneous albinism 2
PTCH1:	patched1
PTCH2:	patched2
PMS2:	postmeiotic segregation increased 2
RECQL4:	RecQ protein-like 4
RTS:	Rothmund–Thomson syndrome
SMO:	smoothened
SLC24A5:	solute carrier family 24, member 5
SLC45A2:	solute carrier family 45, member 2
SHH:	sonic hedgehog
SCC:	squamous cell carcinoma
SUFU:	suppressor of fused gene
TGFBR1:	transforming growth factor beta receptor 1
TYR:	tyrosinase
TYRP1:	tyrosinase-related protein 1
UVR:	ultraviolet radiation
WRN/RECQL2:	Werner syndrome, RecQ helicase-like
XP:	xeroderma pigmentosum

with risk factors such as ultraviolet radiation, immunosuppression, viral infections, and radiotherapy, there is a subset of cases in which it occurs in the context of hereditary cancer syndromes. In general, these genetic syndromes fall under several broad categories: those associated with immunodeficiency, those that affect pigmentation, and those that perturb key molecular pathways involved in the pathogenesis of NMSCs. This article is an overview of the clinical features, epidemiology, evaluation, genetics, and management of the major hereditary genodermatoses with NMSC predisposition (Table I). While the risk of NMSC is increased in many hereditary conditions associated with immunodeficiency, this article focuses on those with the most direct risk of skin cancer.

FAMILIAL CANCER SYNDROMES AND NONMELANOMA SKIN CANCER RISK: INCREASED RISK OF BASAL CELL CARCINOMA

Key points

- **Basal cell nevus syndrome is an autosomal dominant syndrome driven by aberrant activation of the sonic hedgehog pathway; it is characterized by developmental defects and multiple neoplasms, including the development of numerous basal cell carcinomas**
- **Developmental defects in patients with basal cell nevus syndrome include palmar and plantar pits, craniofacial anomalies, corpus collosum dysgenesis, falx cerebri calcification, coarse facies, cleft palate, and spina bifida occulta**
- **Extracutaneous neoplasms in patients with basal cell nevus syndrome include medulloblastomas, rhabdomyosarcomas, odontogenic keratocysts, fibrosarcomas, meningiomas, cardiac fibromas, and ovarian fibromas**
- **Bazex-Dupré-Christol syndrome and Rombo syndrome are rare genetic disorders that have a high degree of phenotypic overlap and are associated with increased risk of basal cell carcinoma**

Basal cell nevus syndrome (Gorlin syndrome, Gorlin–Goltz syndrome, and nevoid basal cell carcinoma)

Basal cell nevus syndrome (BCNS) is an autosomal dominant disorder characterized by the development of multiple neoplasms (including BCCs, medulloblastomas, rhabdomyosarcomas, odontogenic keratocysts, fibrosarcomas, meningiomas, cardiac fibromas, and ovarian fibromas) and developmental defects (including palmar and plantar pits, craniofacial anomalies [eg, macrocephaly and frontal bossing], corpus collosum dysgenesis, falx cerebri calcification, coarse facies, cleft palate, bifid ribs, and spina bifida occulta).[2-7]

Cutaneous findings. The hallmark of BCNS is the development of multiple BCCs; although some patients develop >1000 BCCs over their lifetimes and rare patients fail to develop any, the median number in affected individuals is 8. BCCs can appear as early as the first year of life and develop